Citation:

Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: A population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3; 50 (1): 14-21. Epub 2007 Jun 18.

PubMed ID: 17601539

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess whether high dietary glycemic load and glycemic index were associated with an increased risk of cardiovascular disease in Dutch women consuming modest glycemic load diets, and whether this association was modified by BMI.

Inclusion Criteria:

Women aged 49-70, recruited among breast cancer screening participants in the Prospect-EPIC cohort, one of two Dutch contributions to the EPIC study.

Exclusion Criteria:

- Women who did not consent to linkage with vital status registries (N=355)
- Women with missing questionnaires (N=117)
- Women who reported an energy intake <500kcal per day or >6,000kcal per day (N=92)
- Women with a history of coronary heart disease or cerebrovascular disease (N=628)
- Women with established diabetes (N=451).

Description of Study Protocol:

Recruitment

Between 1993 and 1997, 17,357 women (aged 49-70) were recruited among breast cancer screening participants in the Prospect-EPIC cohort, one of two Dutch contributions to the EPIC (European Prospective Investigation into Cancer and Nutrition) study.

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

- Food intake was assessed using validated 178-item food-frequency questionnaire (FFQ)
- Glycemic index and glycemic load calculated using the glycemic index, carbohydrate content and frequency of intake of individual foods.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- Baseline characteristics in quartiles of energy-adjusted dietary glycemic load were inspected using ANOVA for continuous variables and a chi-square test for categorical variables
- Person-years of follow-up were calculated for each participant from the date of return of the questionnaire to the date of coronary heart disease or cerebrovascular accident diagnosis, the date of death or January 1, 2005
- Cox regression was used to estimate hazard ratios within quartiles of glycemic load and glycemic index using the lowest quartile as reference
- Linear trends across quartiles of glycemic load and glycemic index were determined by including quartiles in the model as a linear covariate
- Associations of glycemic load and glycemic index with biomarkers were determined by linear regression using multivariate models.

Data Collection Summary:

Timing of Measurements

- General questionnaire containing questions on demographic characteristics, presence of chronic diseases and their risk factors was completed at baseline
- Food-frequency questionnaire completed during the year preceding enrollment
- Follow-up on mortality was complete until January 1, 2005.

Dependent Variables

Incident cardiovascular disease; data on morbidity was obtained from the Dutch Centre for Health Care Information, and information on vital status was obtained through linkage with the municipal administration registries.

Independent Variables

- Food intake was assessed using validated 178-item FFQ
- Glycemic index and glycemic load calculated using the glycemic index, carbohydrate content and frequency of intake of individual foods.

Control Variables

- Age
- Smoking

- Pack-years
- Hypertension (HTN)
- Hypercholesterolemia
- Height, weight, BMI
- Mean systolic blood pressure (SBP)
- Total physical activity
- Menopausal status
- Hormone replacement therapy (HRT) and oral contraceptive use
- Nutritional variables (total energy, vitamin E, multivitamins, alcohol, protein, fiber, folate, saturated fat, monounsaturated fat, polyunsaturated fat)
- Waist-hip ratio.

Description of Actual Data Sample:

- *Initial N:* 17,357 women in original cohort
- *Attrition (final N):* 15,714 women after exclusion criteria applied
- *Age:* 49-70 years
- *Ethnicity:* Not mentioned
- *Other relevant demographics:* None
- *Anthropometrics:* None
- *Location:* The Netherlands.

Summary of Results:

Adjusted Hazard Ratios of Cardiovascular Disease According to Quartiles of Energy-Adjusted Dietary Glycemic Load and Glycemic Index Among 15,714 Women

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for Trend
Glycemic Load					
Cases	189	193	198	219	
Crude	1.00	1.02 (0.83-1.24)	1.04 (0.85-1.27)	1.14 (0.94-1.39)	0.175
Model 1: Age	1.00	0.94 (0.77-1.15)	0.93 (0.76-1.13)	0.99 (0.81-1.20)	0.91
Model 2: Multivariate	1.00	1.08 (0.89-1.33)	1.10 (0.90-1.35)	1.20 (0.98-1.47)	0.082
Model 3: Model 2+Nutrients	1.00	1.01 (0.82-1.26)	1.02 (0.80-1.28)	1.12 (0.86-1.45)	0.40
Model 4: Model 3+All Fat	1.00	1.13 (0.89-1.42)	1.21 (0.92-1.60)	1.47 (1.04-2.09)	0.033
Glycemic Index					

Cases	180	201	190	228	
Crude	1.00	1.12 (0.91-1.37)	1.06 (0.86-1.30)	1.28 (1.05-1.55)	0.029
Model 1: Age	1.00	1.07 (0.88-1.31)	1.06 (0.86-1.30)	1.42 (1.17-1.73)	0.001
Model 2: Multivariate	1.00	1.15 (0.94-1.40)	1.13 (0.92-1.39)	1.42 (1.16-1.73)	0.001
Model 3: Model 2+Nutrients	1.00	1.11 (0.90-1.37)	1.09 (0.88-1.35)	1.36 (1.09-1.69)	0.012
Model 4: Model 3+All Fat	1.00	1.11 (0.90-1.36)	1.08 (0.87-1.35)	1.33 (1.07-1.67)	0.020

Key Findings

- During 9±2 years of follow-up (141,633 person-years), 556 cases of coronary heart disease and 243 cases of cerebrovascular accident occurred
- Dietary glycemic load (mean=100±17) was associated with increased risk of cerebrovascular accident, adjusted for cardiovascular disease risk factors and dietary variables, with a hazard ratio (HR) for the highest against the lowest quartile of 1.47 (95% CI: 1.04-2.09, P for trend=0.03)
- Similar results were observed for dietary glycemic index with a corresponding HR of 1.33 (95% CI: 1.07-1.67, P for trend=0.02)
- Glycemic load tended to be associated with both coronary heart disease (HR=1.44, 95% CI: 0.95-2.19, P for trend=0.14) and cerebrovascular accident (HR=1.55, 95% CI: 0.81-2.97, P for trend=0.10), but glycemic index only with coronary heart disease (HR=1.44, 95% CI: 1.10-1.89, P for trend=0.01)
- Among overweight women (BMI>25kg/m^2), glycemic load was associated with cardiovascular disease (HR=1.78, 95% CI: 1.11-2.85, P for trend=0.04), but not among normal weight women (P for interaction=0.19)
- BMI did not modify the association of glycemic index with cardiovascular disease.

Author Conclusion:

- High dietary glycemic load and glycemic index increase the risk of cardiovascular disease, also in a population consuming a modest glycemic load diet
- For glycemic load, this association was similar for coronary heart disease and cerebrovascular accidents, while glycemic index seems particularly associated with coronary heart disease
- These harmful effects may particularly affect overweight women.

Reviewer Comments:

- *Adjusted for several risk factors*
- *Food-frequency questionnaires completed the year preceding enrollment*

- *Authors note the following limitations:*
  - *Limited generalizability to men*
  - *Residual confounding by unknown risk factors*
  - *FFQ not designed to estimate dietary glycemic load*
  - *Concept of glycemic load and glycemic index is criticized for limited applicability in daily practice.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**		Yes
	1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
	1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
	1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**		Yes
	2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
	2.2.	Were criteria applied equally to all study groups?	Yes
	2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
	2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**		Yes

	3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
	3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
	3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
	3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
	3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
	3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**		Yes
	4.1.	Were follow-up methods described and the same for all groups?	Yes
	4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
	4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
	4.4.	Were reasons for withdrawals similar across groups?	N/A
	4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**		Yes
	5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
	5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
	5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
	5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
	5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**		Yes
	6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
	6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
	6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
	6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
	6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
	6.6.	Were extra or unplanned treatments described?	N/A
	6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
	6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
	7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	No
	10.2.	Was the study free from apparent conflict of interest?	Yes